(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 364 819 A3**

(12) **EUROPEAN PATENT APPLICATION**

(21) Application number: **89118460.8**

(51) Int. Cl.5: **C07K 7/20**, A61K 37/02

(22) Date of filing: **05.10.89**

(30) Priority: **21.10.88 US 260994**
07.09.89 US 404667

(43) Date of publication of application:
25.04.90 Bulletin 90/17

(84) Designated Contracting States:
AT BE CH DE ES FR GB GR IT LI LU NL SE

(88) Date of deferred publication of the search report:
06.03.91 Bulletin 91/10

(71) Applicant: **THE ADMINISTRATORS OF THE TULANE EDUCATIONAL FUND**
1430 Tulane Avenue
New Orleans, LA 70112(US)

(72) Inventor: **Schally, Andrew V.**
5025 Kawanne Avenue
Metairie, LA 70002(US)
Inventor: **Bajuz, Sandor**
Derek ut 16/a
H-1016 Budapest(HU)
Inventor: **Janaky, Tamas**
3912 Hessmer Avenue
Metairie, LA 70002(US)

(74) Representative: **Dr. Fuchs, Dr. Luderschmidt**
Dipl.-Phys. Seids, Dr. Mehler Patentanwälte
Abraham-Lincoln-Strasse 7
W-6200 Wiesbaden(DE)

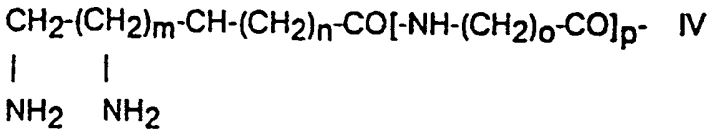
(54) **LHRH analogs.**

(57) The present invention deals with LHRH analogues which contain cytotoxic moieties and have influence on the release of gonadotropins from the pituitary gland of mammals, including humans. The compounds of this invention are represented by the formula:
X-R^1-R^2-R^3-Ser-R^5-R^6(Q)-Leu-Arg-Pro-R^{10}-NH_2
wherein
R^1 is pGlu, Pro, D-Nal(2), or D-Phe(4Cl),
R^2 is His or D-Phe(4Cl),
R^3 is Trp, D-Trp or D-Pal(3),
R^5 is Tyr or Arg,
R^6 is D-Phe or R'^6,where R'^6 is D-Orn, D-Lys or D-Phe(NH_2),
R^{10} is Gly or D-Ala,
X is hydrogen, a lower alkanoyl group of 2-5 carbon atoms or carbamyl,
Q is bis-(2-chloroethyl)amino group provided that R^6 is D-Phe,
where R^5 is R'^6,
Q is a complexed metal-containing acyl group having the formula:

$$[(Q')(A)] \text{ or } [(Q'')(B)_2(A)]$$
$$\text{II} \qquad \text{III}$$

wherein
Q' is $Pt(Y)_2$, where Y is an anion derived from a pharmaceutically acceptable acid,
A is a diaminoacyl group having the formula

EP 0 364 819 A3



where
m is 0 or 1,
n and p are 0-10,
o is 1-10,
Q^{α} is a non-platinum-group metal, either a main-group metal such as gallium, germanium, and tin, or a transition metal such as titanium, vanadium, iron, copper, cobalt, gold, nickel, cadmium and zinc,
B is a aralkylidene, heteroaralkylidene, cycloalkylidene or heterocycloalkylidene group containing oxygen anion or carboxylate anion at position 2 or 3, and pharmaceutically acceptable salts thereof and methods of use pertaining these compounds.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 89 11 8460

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
A	INT. J. PEPT. PROT. RES., vol. 32, no. 1, 1988, pages 56-63; A. RICOUART et al.: "Photosubstitution of cymantrenylalanine as a tool in peptide chemistry" * Pages 56-57, column 1 *	1,5-10	C 07 K 7/20 A 61 K 37/43
D,A	CHEMICAL ABSTRACTS, vol. 94, 1981, page 49, abstract no. 11195j, Columbus, Ohio, US; K. CHANNABASAVAIAH et al.: "New potent agonist and antagonist analogs of luteinizing hormone releasing hormone", & PEPT., STRUCT. BIOL. FUNCT., PROC. AM. PEPT. SYMP., 6TH 1979, 803-6	1-4	
A	J. ENDOCRINOL. INVEST., vol. 11, 1988, pages 535-567; B.J.A. FURR et al.: "Luteinizing hormone-releasing hormone and its analogues: a review of biological properties and clinical uses" * Page 540, column 2 - page 544, column 1 *	1-10	
P,X	PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE USA, vol. 86, no. 16, August 1989, pages 6313-6317, Washington, DC, US; S. BAJUSZ et al.: "Highly potent metallopeptide analogues of luteinizing hormone-releasing hormone" * Entire article *	1,5-10	TECHNICAL FIELDS SEARCHED (Int. Cl.5) C 07 K A 61 K
P,X	PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE USA, vol. 86, no. 16, August 1989, pages 6318-6322, Washington, DC, US; S. BAJUSZ et al.: "Highly potent analogues of luteinizing hormone-releasing hormone containing D-phenylalanine nitrogen mustard in position 6" * Entire article *	1-4	

The present search report has been drawn up for all claims

Place of search	Date of completion of search	Examiner
The Hague	28 November 90	GROENENDIJK M.S.M.

CATEGORY OF CITED DOCUMENTS

X: particularly relevant if taken alone
Y: particularly relevant if combined with another document of the same catagory
A: technological background
O: non-written disclosure
P: intermediate document
T: theory or principle underlying the invention

E: earlier patent document, but published on, or after the filing date
D: document cited in the application
L: document cited for other reasons

&: member of the same patent family, corresponding document